

## WHAT IS CLAIMED:

1. A transgenic mouse homozygous for a disrupted PTP-1B gene wherein the mouse shows a phenotype of an altered response to insulin as compared to wild-type mice.
2. The mouse of claim 1 wherein the PTP-1B gene is disrupted by the insertion of a plasmid comprising a selectable marker gene.
3. The mouse of claim 2 wherein the PTP-1B gene is disrupted by the insertion of pTARGET.
4. The mouse of claim 1 wherein the mouse has about half the weight gain of wild-type mice when fed a high fat, high carbohydrate diet.
5. The mouse of claim 1 wherein the mouse has about half the level of circulating insulin in the fed state as compared to wild-type mice.
6. The mouse of claim 1 wherein the mouse has about 13% of the level of blood glucose in the fed state as compared to wild-type mice.
7. A cell line derived from the mouse of claim 1.
8. A method of producing a mouse, at least some of whose cells contain an altered gene encoding an altered form of protein tyrosine phosphatase-1 (PTP-1), the altered gene having been targeted to replace the wild-type PTP-1B gene in the mouse, the method comprising:
  - (a) providing an altered gene encoding an altered form of PTP-1B designed to target the PTP-1B gene of mouse embryonic stem (ES) cells;
  - (b) introducing the altered gene encoding an altered form of PTP-1B into mouse ES cells;
  - (c) selecting ES cells in which the altered gene encoding an altered form of PTP-1B has disrupted the wild-type PTP-1B gene;
  - (d) injecting the ES cells from step (c) into mouse blastocysts;

(e) implanting the blastocysts from step (d) into a pseudopregnant mouse;

(f) allowing the blastocysts to develop into embryos and allowing the embryos to develop to term in order to produce a mouse at least some of whose cells contain an altered gene encoding an altered form of PTP-1.

9. A method of identifying inhibitors of the enzymatic activity of PTP-1B comprising:

- 10 (a) providing an enzymatically active preparation of PTP-1B;  
(b) measuring the enzymatic activity of PTP-1B in the enzymatically active preparation of PTP-1B in the presence and in the absence of a substance suspected of being an inhibitor of the enzymatic activity of PTP-1B;  
where a decrease in the enzymatic activity of PTP-1B in the presence as compared to the absence of the substance indicates that the substance is an inhibitor of the enzymatic activity of PTP-1B.

10. The method of claim 9 where the substance is obtained from a library of compounds.

11. A method of identifying inhibitors of the enzymatic activity of the PTP-1B protein comprising:

- 20 (a) transfecting a cell with DNA encoding the human PTP-1B protein;  
(b) culturing the cells of step (a) under conditions such that PTP-1B protein is produced;  
25 (c) measuring the enzymatic activity of the PTP-1B protein in the presence and in the absence of a substance suspected of being an inhibitor of the enzymatic activity of the PTP-1B protein;  
where a decrease in the enzymatic activity of the PTP-1B protein in the presence as compared to the absence of the substance indicates that the substance is an inhibitor of the enzymatic activity of the PTP-1B protein.

12. The method of claim 9 where the substance is obtained from a library of compounds.

35

13. An inhibitor of the enzymatic activity of PTP-1B identified by the method of claim 10.

14. A method of determining whether a substance modulates glucose or triglyceride levels in a mammal that comprises:
- (a) providing an enzymatically active preparation of PTP-1B;
  - (b) measuring the enzymatic activity of PTP-1B in the enzymatically active preparation of PTP-1B in the presence and in the absence of a substance suspected of being an inhibitor of the enzymatic activity of PTP-1B, thus identifying a substance that is an inhibitor of the enzymatic activity of PTP-1B; where a decrease in the enzymatic activity of PTP-1B in the presence as compared to the absence of the substance indicates that the substance is an inhibitor of the enzymatic activity of PTP-1B;
  - (c) administering the substance that is an inhibitor of the enzymatic activity of PTP-1B to a mammal;
  - (d) measuring the blood glucose level or triglyceride levels of the mammal in step (c) and comparing the blood glucose level or triglyceride levels of the mammal in step (c) with the blood glucose level or triglyceride levels of a mammal that has not been administered the substance that is an inhibitor of the enzymatic activity of PTP-1B; where a difference in the blood glucose level or triglyceride levels of the mammal in step (c) as compared with the blood glucose level or triglyceride levels of the mammal that has not been administered the substance that is an inhibitor of the enzymatic activity of PTP-1B indicates that the substance modulates glucose or triglyceride levels in a mammal.

15. The method of claim 14 where the mammal is a mouse or human.

16. A method of determining whether a substance regulates obesity in a mammal that comprises:
- (a) providing an enzymatically active preparation of PTP-1B;
  - (b) measuring the enzymatic activity of PTP-1B in the enzymatically active preparation of PTP-1B in the presence and in the absence of a

substance suspected of being an inhibitor of the enzymatic activity of PTP-1B, thus identifying a substance that is an inhibitor of the enzymatic activity of PTP-1B;

where a decrease in the enzymatic activity of PTP-1B in the presence as compared to the absence of the substance indicates that the substance is an inhibitor of the enzymatic activity of PTP-1B;

(c) administering the substance that is an inhibitor of the enzymatic activity of PTP-1B to a mammal;

(d) measuring the weight gain of the mammal in step (c) when the mammal of step (c) is fed a high fat, high carbohydrate diet and comparing the weight gain of the mammal in step (c) with the weight gain of a mammal fed a high fat, high carbohydrate diet that has not been administered the substance that is an inhibitor of the enzymatic activity of PTP-1B;

where a difference in the weight gain of the mammal in step (c) as compared with the weight gain of the mammal that has not been administered the substance that is an inhibitor of the enzymatic activity of PTP-1B indicates that the substance regulates obesity in a mammal.

17. The method of claim 16 where the mammal is a mouse or human.

18. A method of determining whether a substance modulates glucose or triglyceride levels in a mammal that comprises:

(a) transfecting a cell with DNA encoding the human PTP-1B protein;

(b) culturing the cells of step (a) under conditions such that PTP-1B protein is produced;

(c) measuring the enzymatic activity of the PTP-1B protein in the transfected cells in the presence and in the absence of a substance suspected of being an inhibitor of the enzymatic activity of the PTP-1B protein;

where a decrease in the enzymatic activity of the PTP-1B protein in the presence as compared to the absence of the substance indicates that the substance is an inhibitor of the enzymatic activity of the PTP-1B protein;

(d) administering the substance that is an inhibitor of the enzymatic activity of PTP-1B to a mammal;

(e) measuring the blood glucose level or triglyceride levels of the mammal in step (d) and comparing the blood glucose level or triglyceride levels of the mammal in step (d) with the blood glucose level or triglyceride levels of a mammal that has not been administered the substance that is an inhibitor of the enzymatic activity of PTP-1B;

where a difference in the blood glucose level or triglyceride levels of the mammal in step (d) as compared with the blood glucose level or triglyceride levels of the mammal that has not been administered the substance that is an inhibitor of the enzymatic activity of PTP-1B indicates that the substance modulates glucose or triglyceride levels in a mammal.

19. The method of claim 18 where the mammal is a mouse or human.

20. A method of determining whether a substance regulates obesity in a mammal that comprises:

(a) transfecting a cell with DNA encoding the human PTP-1B protein;

(b) culturing the cells of step (a) under conditions such that PTP-1B protein is produced;

(c) measuring the enzymatic activity of the PTP-1B protein in the transfected cells in the presence and in the absence of a substance suspected of being an inhibitor of the enzymatic activity of the PTP-1B protein;

where a decrease in the enzymatic activity of the PTP-1B protein in the presence as compared to the absence of the substance indicates that the substance is an inhibitor of the enzymatic activity of the PTP-1B protein;

(d) administering the substance that is an inhibitor of the enzymatic activity of PTP-1B to a mammal;

(e) measuring the weight gain of the mammal in step (d) when the mammal of step (d) is fed a high fat, high carbohydrate diet and comparing the weight gain of the mammal in step (d) with the weight gain of a mammal fed a high fat, high carbohydrate diet that has not been administered the substance that is an inhibitor of the enzymatic activity of PTP-1B;

where a difference in the weight gain of the mammal in step (d) as compared with the weight gain of the mammal that has not been administered the

substance that is an inhibitor of the enzymatic activity of PTP-1B indicates that the substance regulates obesity in a mammal.

21. The method of claim 20 where the mammal is a mouse or  
5 human.

22. A method of treating obesity comprising administering an inhibitor of the enzymatic activity of PTP-1B to an obese mammal.

10 23. A method of treating Type II diabetes and associated complications comprising administering an inhibitor of the enzymatic activity of PTP-1B to a person with Type II diabetes.